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March 12, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 8301-r edited final.doc).

Title: Neuromuscular interactions around the knee in children, adults and elderly

Author: Eleftherios Kellis, Lida Mademli, Dimitrios Patikas, Nikolaos Kofotolis

Name of Journal: *World Journal of Orthopaedics*

ESPS Manuscript NO: 8301

The manuscript has been improved according to the suggestions of reviewers:

Reviewer 1:

1 Format has been updated, [as requested](#)

Comments:

1. The manuscript provides an overview of the neuromuscular mechanisms associated with knee joint injuries in children, adults and elderly. It reports current evidences that indicate the existence of similarities in the neuromuscular mechanisms by which children and elderly differ compared with young adults. The topic presented by the authors is adapted to the readership of the World J Orthopaedics. The manuscript is globally very interesting, very well structured and written. It is also very well documented with 177 references which constitute the body of the review. Therefore, I strongly recommend the manuscript for publication.

Response: Thank you

2. I have one single remark and several minor comments that may further improve the quality of the manuscript. The authors focused their review on single knee joint analysis. It is a pity that authors did not report the results of studies (if any) on the effect of single (or bilateral) knee injury on functional whole-body motor tasks, e.g. tasks requiring a postural control as during the maintenance of quiet standing, upper arm movement from the erect posture, gait initiation, level walking and so forth. For such motor tasks, it is possible that adaptive changes occur in non-injured muscles (e.g. at the ankle or hip level) to compensate for the reduced strength capacity of the injured knee and maintain an optimal “global” motor output (in terms of postural stability or motor performance). Such adaptive capacity of the postural system to internal (and external) constraints has recently been emphasized in the literature (e.g. Yiou et al. 2012 World J Orthopaedics for recent review). This “whole body” level of analysis was not envisaged by the authors.

Response: Although we agree that understanding neuromuscular strategies in whole body movement tasks is a very important element a critical decision has been made to focus on single – joint or isolated (strength testing) conditions because, first and most importantly it better reflects our research work and therefore expertise in this area and, second, a preliminary search of the literature indicated that such a wide topic would be very difficult to be covered within a given manuscript length. Again, we agree with this comment and this is the main reason why this particular focus of the study is mentioned both in the Introduction and Conclusion Sections of the paper.

P3 L26: CNS might be in bracket after “central nervous system” at this place since it is the first time it is used in the manuscript. Now, the abbreviation might also be removed since it is very rarely used in the manuscript.

Response: We agree with this comment. The “CNS” was removed.

P4 L10: “single joint moment” may be replaced by “single joint movement”

Response: We agree. This was replaced, as suggested (Page 4, line 5).

P5 L14: Authors state that “patellar dislocations typically occur in young adults during sport” without specifying the sports involved. Are there sports particularly at risks?

Response: This sentence is based on the study by Atkin et al. (2000) who monitored only sport participation in general, without specifying the type of sports involved.

P6 L8: it should be stated here that “BMI” is “body mass index”

Response: “BMI” was replaced by “Body mass index”(Page 9, line 1)

P8 L2: “imflammation” should be “inflammation”

Response: It was replaced, as requested (page 10, 4 lines from bottom)

P8 L10: “MNair” should be “McNair”

Response: We agree. It was revised, as suggested (Page 11, Line 4).

P9 L1: What kinds of “techniques” to increase the Quadriceps activation the authors refer to?

Response: An example may be electrical stimulation. This is now reported in the paper (Page Page 11, 4th line from bottom).

P9 L7: it should be stated that “s” is “surface”.

Response: It is now mentioned, as suggested (Page 12, line 2).

P9 L9 second paragraph: please remove the “and” (“some studies have reported [and] an earlier onset”

Response: It was deleted, as requested.

P10 L3 second paragraph: “as well its effect” should be “as well as its effect”

Response: We agree. It was revised (Page 13, line 6).

P12 first paragraph: authors refer here to the H:Q ratio in “athletes” and “players”: please state what athletes or players.

Response: players is the correct word and it is now revised (Page 14, 7th line from bottom).

批注 [dp1]: Εδώ ζητάει και το είδος του αθλήματος

P15 L1: State that “MTU” is “muscle tendon unit” here since it is the first time it is used in the manuscript.

Response: We agree. The abbreviation is now defined (Page 19, line 10) .

P15 L3: State what is “CSA”

Response: It is now stated (Cross sectional area) (Page 19, line 13)

P17 L5: Check for the references in bracket.

Response: ???Corrected (Page 21, line 19).

P18 L7: State here that the “specific tension” is the ratio between muscle strength and size (and remove the definition which appear later at the bottom of the page)

Response: Specific tension is now defined in this paragraph and it was deleted by the bottom of the page (Page 24, 5th line from bottom).

P18 L4 last paragraph: authors state that "the reported-age related decrease in the measured isometric force/moment ranges from 19% to 38%". For what category of age?

Response: In order to report for what category of age this age-related decrease in muscle strength is referred to, the ages of the subjects participating in the reported studies are now included in Table 1. Briefly, the age of the young adults ranges from 20 to 35 yrs and of the old adults from 60 to 75.

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P19 L8: it is not clear what is the "retardation" of the biarticular muscles

Response: Retardation of the biarticular muscles refers to the deterioration of these muscles. The word retardation has been replaced by "deterioration" in the revised manuscript (Page 24, 4th line from bottom).

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P22 first sentence: "on" is missing ("on" the capacity to produce ...) **Response:** "on" is now added.

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P22 L3 second paragraph: VL should be vastus

Response: "VL" was replaced by vastus lateralis

Reviewer 2

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Article is related to orthopedic journal but more suitable to submit in any physiology journal

Response: This is related to Journal's policy and we cannot comment.

Reviewer 3

This is a good review of the current knowledge of "Age differences in knee neuromuscular function". My major concern is that the authors are not addressing sex differences in neuromuscular function sufficiently. Especially during puberty significant differences in neuromuscular activation/strategies (co-contraction) between boys and girls occur. This certainly has an influence on levels of physical activity and injury risks. I think that this review should focus on healthy children, adults, and elderly. Neuromuscular activation strategies after knee injuries should be a different review topic. Please comment.

Response:

Response: We agree with the reviewer's comment regarding the sex differences in the level of activation of the thigh muscles. Indeed, sex plays an important role in the level of activation, during dynamic movements. Young females (puberty / post-puberty) show higher quadriceps activation than males and lower activation on the medial muscles of the knee extensors and flexors. These imbalances observed in females could increase

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their risk for injury. This piece of information with the respective references, have been added in the text (page ?? lines ??). However, in younger ages (pre-puberty), and during single-joint movements, no sex differences have been observed.

Concerning older adults, to our knowledge there is no information on the effect of gender on the neuromuscular function of the knee joint. Most of the studies investigating the neuromuscular function involve only women, men; or groups composed of both men and women, without any direct comparison between genders. When comparing the results of men and women between different studies, no gender-related differences can be observed. Furthermore, studies conducted on women or men generalize their findings for all the aged population. Nevertheless, there are gender specific differences concerning age related reduction in muscle strength. The revised manuscript reports how gender differences influence the age related reduction in muscle strength (pages 17 -18 and 21-23 in the new version of the paper).

This review paper does focus mainly on the neuromuscular strategies in children, elderly and adults. However, we think that there is often a missing link to relate findings on “normal” neuromuscular strategies with either strategies that often lead to injury or injury profiles or both. In this respect, this approach may provide a stimulus for inter-disciplinary approach to examine injury profiles, their cause and subsequent rehabilitation.

Reviewer 4

This is a well written and documented paper. There are several typos that have been indicated in red in the text or directly edited. There are few questions.

Page 15. Concerning the analysis of fiber types in children, what were the muscles studied in the two papers cited?

Response: Bell et al. 1980 examined the vastus lateralis, whereas Brooke and Engel (1979) examined muscles of 16 young patients (mean age 8.4years), with no clinical evidence of disease in the muscle biopsied, and a neuromuscular system closest to normal. Unfortunately, this early study does not explicitly specify the names of the examined muscles, however, vastus lateralis, biceps femoris, gastrocnemius and deltoid are some of the muscles that are mentioned.

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Page 16. The author wrote that there is no data available concerning the hamstring muscles in children and adults in the current literature. Is he referring to the CSA, the physiological CSA, or the pennation angle?

Response:

Response: It concerns the pennation angle. This has been added in the new version (Page 19).

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Reviewer 5

This is a nice review in a relevant topic. The content seem to be sound. Unfortunately there is no information on the workflow of the Metanalysis (CONSORT-Statement, which keywords have been screened in which databased like PubMed) available or any description of inclusion/exclusion criteria for papers evaluated. This in a significant limitation for a fair review and should be standard for review-publications. I would like to encourage the authors to add this information in a "Material and Methods"-section and resubmit.

Response: We agree and we accept the comment. A new section "Materials and Methods" was added to analyze the review process.

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2 Revision has been made according to the suggestions of the reviewer

(1)??

(2)??

(3)??

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3 References and typesetting were corrected

Thank you again for publishing our manuscript in the *World Journal of Orthopaedics*

Sincerely yours,



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~~Yours Sincerely,~~